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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,981	01/26/2006	Shigeyoshi Nishino	740709-551	9439
22204 NIXON PEABODY, LLP 401 9TH STREET, NW SUITE 900 WASHINGTON, DC 20004-2128	7590 05/28/2008		EXAMINER WILLIS, DOUGLAS M	
			ART UNIT 4161	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/565,981

Applicant(s)

NISHINO ET AL.

Examiner

DOUGLAS M. WILLIS

Art Unit

4161

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7 and 8 is/are rejected.
- 7) ☒ Claim(s) 6 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SI/CC)
Paper No(s)/Mail Date 1-26-06; 7-26-06; 9-26-06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims / Priority

1. Claims 1-8 are pending in the current application. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/JP2004/10965, filed July 30, 2004, which claims priority under 35 U.S.C. § 119(a) to JP 2003-282696, filed July 30, 2003.

A first action on the merits of claims 1-8 is contained within.

Claim Objections

Claim 6 is objected to because of the following informalities: ammonium acetate is not an ammonium *carbonate*. The examiner interprets the term *carbonate* to mean *carboxylate* in order to remain accurate and consistent with preceding claim language. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5 and 6 are rejected under 35 U.S.C. § 102(a) as being anticipated by WO 03/064399.

The instant application recites a process for preparation of 6,7-bis(2-methoxyethoxy)quinazoline-4-one, which comprises causing a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with a formic acid compound in the presence of an ammonium

carboxylate [claim 1], wherein the formic acid compound is an orthoformic ester [claim 5] and the ammonium carboxylate is ammonium acetate [claim 6].

WO 03/064399, in the English translation provided by the examiner, teaches the preparation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one by causing a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with methyl orthoformate in the presence of ammonium acetate [example I19; p. 36].

The foreign priority papers do not obviate this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 2-4, 7 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Katsuyuki, et al. in JP 2002-293773, in view of Bakalova et al. and Smith, Organic Chemistry, 1st Edition.

The instant application recites the following:

Claim 2 - a process for the preparation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, which comprises the steps in order of: 1) Step 1 - a reaction of ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate with hydrogen in the presence of a metallic catalyst to prepare ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate; and 2) Step 2 - a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with a formic acid compound in the presence of an ammonium carboxylate to prepare 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one;

Claim 3 - a process for the preparation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, which comprises the steps in order of: 1) Step 1 - a reaction of ethyl 3,4-bis(2-methoxyethoxy)benzoate with nitric acid in the presence of sulfuric acid to prepare ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate; 2) Step 2 - a reaction of ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate with hydrogen in the presence of a metallic catalyst to prepare ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate; and 3) Step 3 - a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with a formic acid compound in the presence of an ammonium

carboxylate to prepare 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one; and

Claim 4 - a process for the preparation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, which comprises the steps in order of: 1) Step 1 - a reaction of ethyl 3,4-dihydroxybenzoate with 2-chloroethyl methyl ether in an organic solvent in the presence of a base to prepare ethyl 3,4-bis(2-methoxyethoxy)benzoate; 2) Step 2 - a reaction of ethyl 3,4-bis(2-methoxyethoxy)benzoate with nitric acid in the presence of sulfuric acid to prepare ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate; 3) Step 3 - a reaction of ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate with hydrogen in the presence of a metallic catalyst to prepare ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate; and 4) Step 4 - a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with a formic acid compound in the presence of an ammonium carboxylate to prepare 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one;

Furthermore, the instant application recites a process, according to Step 1 of claim 3 or Step 2 of claim 4 above, wherein: a) the temperature range is 45-75 °C [claim 7] and b) 1-2.9 % w/w Pt/C is used as the metallic catalyst [claim 8].

Katsuyuki (JP 2002-293773), in the English translation provided by the examiner, teaches a process for the preparation of 4-hydroxy-6,7-bis(2-methoxy-ethoxy)quinazoline, a prototropic 1*H* tautomer of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one [concept of tautomerism in Smith, p. 817; structure in Bakalova, Scheme 2, p.230], which involves the following four steps in sequence [¶19, p. 5]: 1) Step 1 - a reaction of ethyl 3,4-dihydroxybenzoate with 2-methoxyethyl methanesulfonate, tetrabutylammonium iodide catalyst, and potassium carbonate base in acetone solvent to prepare ethyl 3,4-bis(2-methoxyethoxy)benzoate [¶7-10, p. 5]; 2) Step 2 - a reaction of ethyl 3,4-bis(2-

methoxyethoxy)benzoate with nitric acid in the presence of sulfuric acid in acetic acid solvent to prepare ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate [¶11-12, p. 5]; 3) Step 3 - a reaction of ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate with hydrogen in the presence of a platinum catalyst in methanol solvent to prepare ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate [¶13-15, p. 6]; and 4) Step 4 - a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with ammonium formate in dimethyl formamide solvent to prepare 6,7-bis(2-methoxyethoxy)quinazoline-4-one [¶16-19, p. 6].

The four steps in sequence, indicated above, are the same four steps claimed in the instant application. More importantly, these steps, when considered in part, entirely comprise all procedural limitations set forth and recited in claims 3 and 4 of the instant application. The only differences between the applicant's recited processes and those of the reference are experimental parameters. For example, in Step 1 of claim 4 in the instant application, 2-chloroethyl methyl ether and dimethyl formamide are used as the alkylating agent and solvent, respectively, whereas 2-methoxyethyl methanesulfonate and acetone assume these roles in the reference [¶24-25, pp. 7-8]. Similarly, in Step 2 of claim 4, which is synonymous with both Step 1 of claim 2 and Step 2 of claim 3, 45-75 °C is employed as the temperature range for nitration, whereas the reference employs a range of 15-40 °C [¶30-33, p. 8]. Next, in Step 3 of claim 4, which is synonymous with both Step 2 of claim 2 and Step 3 of claim 3, 1-2.9 % w/w Pt/C is utilized as the metallic catalyst, whereas the reference uses 3-10 % w/w Pt/C as the metallic catalyst [¶38, p. 9]; Finally, in Step 4 of claim 4, methyl orthoformate is used as the formic acid compound, whereas ammonium formate serves in this capacity in the reference [¶43-44, pp. 10].

The adjustment of experimental parameters or reaction conditions (e.g. determining result

effective amounts of the reagents beneficially taught by the cited references, especially proximal to or within the broad ranges instantly claimed, such as % w/w used), as well as adjustment of reaction temperature, reaction time, solvent employed and reagent choice, is merely deemed a matter of judicious selection and routine optimization, which is well within the purview of the skilled artisan. (*In re* Mostovych, Weber, Mitchell and Aulbach, 144 USPQ 38) Accordingly, these empirical modifications, undertaken towards process optimization, would have been well within the purview of the skilled artisan, rendering said claims obvious at the time this invention was made.

Claims 1 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mhaske, et al., in view of JP 2002-293773, Bakalova et al. and Smith, Organic Chemistry, 1st Edition.

The instant application recites the following:

Claim 1 - a process for the preparation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, which comprises causing a reaction of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate with a formic acid compound in the presence of an ammonium carboxylate;

Claim 5 - the process according to one of the claims 1 to 4, wherein the formic acid compound is an orthoformic ester;

Mhaske recites a process for the generic preparation of quinazoline-4-ones from anthranilic acids, wherein the following is taught: a) formic acid compounds or orthoformic esters are taught as alternatively usable when reacting with anthranilic acid; and b) the aforementioned reagents further react in the presence of an essential amine/ammonia base to yield a quinazoline-4-one [p. 9791; Scheme 4].

Katsuyuki (JP 2002-293773), as discussed earlier, teaches a process for the preparation of

a prototropic 1/*H* tautomer of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one [concept of tautomerism in Smith, p. 817; structure in Bakalova, Scheme 2, p.230], wherein ammonium formate serves as both the formic acid compound and the ammonium carboxylate (source of necessary amine or ammonia base) [¶16-19, p. 6].

The only differences between the applicant's process and that of the references above are as follows: a) the combination of both a formic acid compound and an ammonium carboxylate in Step 4, as recited in claim 1 of the instant application; and b) the choice of formic acid compound as recited in claim 5 of the instant application.

Since Mhaske teaches that both orthoformic esters and formic acid compounds are alternatively usable in effecting the formation of quinazoline-4-ones via ring closure from anthranilic acids, and Katsayuki teaches both that - 1) anthranilic acid (derivatives) esters can be used in the ring closure, and 2) ammonium formate can serve as both a formic acid compound and an ammonium carboxylate (source of necessary amine or ammonia base) simultaneously in the preparation of 4-hydroxy-6,7-bis(2-methoxy-ethoxy)quinazoline, it would have been obvious to one having ordinary skill in the art at the time this invention was made, to combine an orthoester and a formic acid compound to effect the ring closure and formation of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, especially where ammonium formate is not chosen as the formic acid compound and ammonium carboxylate (source of necessary amine or ammonia base). Thus, based on the essential role played by the formic acid compound and the ammonium carboxylate, including both in the ring closure would provide a reasonable expectation of success, rendering claim 1 obvious.

Similarly, methyl orthoformate, $\text{CH}(\text{OCH}_3)_3$, an orthoformic ester, is recited as the

formic acid compound, whereas Mhaske teaches that orthoformic esters are alternatively usable as formic acid compounds in effecting the formation of quinazoline-4-ones via ring closure from anthranilic acids. Since Katsuyuki teaches that anthranilic acids and their derivatives are alternatively usable in the synthesis of quinazoline-4-ones, it would have been obvious to one having ordinary skill in the art at the time this invention was made, to use an orthoformic ester as a formic acid compound in the formation of quinazoline-4-ones from anthranilic acid esters, with a reasonable expectation of success, rendering claim 5 obvious.

Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mhaske, et al., in view of Katsuyuki, et al. in JP 2002-293773 and Yamamoto, et al. in US 4,096,144.

The instant application recites, in claim 6, a process according to one of the claims 1 to 4, wherein the ammonium *carboxylate* is ammonium acetate.

Mhaske, as discussed above, recites a process for the generic preparation of a quinazoline-4-one from an anthranilic acid, wherein an amine/ammonia base is one of the essential components to effect the ring closure [p. 9791; Scheme 4].

Katsuyuki, as discussed above, teaches a process for the preparation of a prototropic 1*H* tautomer of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, wherein ammonium formate is used as the ammonium carboxylate or essential ammonia source [¶16-19, p. 6].

Yamamoto (US 4,096,144) teaches a process for the preparation of quinazoline derivatives, wherein the ammonia necessary for the ring closure, may be added in the form of the ammonium carboxylate, ammonium acetate [p. 3, column 4, lines 42-47].

Since Mhaske teaches that ammonia or amine bases are essential to effect the ring closure in the formation of quinazoline-4-ones, Katsuyuki teaches the use of an ammonium carboxylate,

ammonium formate, in the preparation of a tautomer of 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, and Yamamoto specifically discloses the ammonium carboxylate, ammonium acetate, as a source of ammonia to effect the ring closure in the formation of quinazoline derivatives, it would have been obvious to one having ordinary skill in the art at the time this invention was made, to employ ammonium acetate as an ammonium carboxylate or ammonia source in the preparation of the quinazoline derivative, 6,7-bis(2-methoxy-ethoxy)quinazoline-4-one, with a reasonable expectation of success, rendering claim 6 obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Friday from 8:00-5:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan, can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Art Unit: 4161

/D. M. W./

Examiner, Art Unit 4161

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4161